COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING VIRAL INFECTIONS AND ASSOCIATED DISEASES

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Field of the Invention

The present invention relates to novel pyridine derivatives, as well as compositions containing such derivatives and their use for treating or preventing viral infections and diseases associated with such infections, particularly those viral infections and associated diseases caused by viruses within the Flaviviridae family.

Background of the Invention

The Flaviviridae family consists of three genera and several viruses that are currently unassigned to specific genera. The hepacivirus genus includes the hepatitis C viruses (HCV). Viruses such as GB virus-A and GB virus-A-like agents, GB virus-B and GBV-C or hepatitis G virus, while at present not formally classified within the hepacivirus genus, are closely related to HCV and represent unassigned members of the Flaviviridae family. Also within the Flaviviridae is the pestivirus genus, which includes bovine viral diarrhea viruses (BVDV), border disease viruses and classical swine fever virus, and the flavivirus genus, with viruses such as dengue, yellow fever, Japanese encephalitis and tick-borne encephalitis viruses.

Viruses within this family cause significant disease in human and animal populations. HCV is a major cause of human

hepatitis globally. The World Health Organization estimates that 170 million people worldwide are presently infected with the virus. Most infections become persistent and about 60% of cases develop chronic liver disease. Chronic HCV infection can lead to development of cirrhosis, hepatocellular carcinoma and liver failure.

Interferon and interferon in combination with ribavirin are used in the U.S. to treat hepatitis caused by HCV. These treatments are associated with improved serum enzyme response in some patients. The remainder are non-responsive to treatment. For responders, a sustained clinical improvement is seen in only a small percentage of patients; the majority of patients relapse upon cessation of treatment. Thus, the effectiveness of therapy for chronic hepatitis C is variable and its cure rate remains low. Moreover, therapy is often associated with considerable side effects.

Pestivirus infections of domesticated livestock cause significant economic losses worldwide. Pestiviruses cause a range of clinical manifestations including abortion, teratogenesis, respiratory problems, chronic wasting disease, immune system dysfunction and predisposition to secondary viral and bacterial infections. Certain BVDV strains cause an acute fatal disease. BVDV can also establish persistent infections in fetuses. When born, these persistently infected (PI) animals remain viremic throughout life and serve as continuous virus reservoirs. PI animals often succumb to fatal mucosal disease.

Flaviviruses are important pathogens of man and are also prevalent throughout the world. There are at least 38 flaviviruses associated with human disease, including the dengue fever viruses, yellow fever virus and Japanese encephalititis virus. Flaviviruses cause a range of acute febrile illnesses and encephalitic and hemorrhagic diseases.

Currently, there are no antiviral pharmaceuticals to prevent or treat pestivirus or flavivirus infections.

New therapies and preventatives are clearly needed for infections and diseases caused by viruses of the Flaviviridae family.

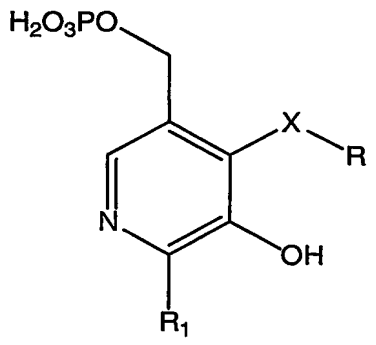
In considering approaches to the diagnosis, control, prevention and treatment of infections and associated diseases caused by viruses, it is often desirable to identify virus-specific functions that may be exploited in the implementation of such approaches. In particular, enzymatic activities of virus-encoded polypeptides are quite useful. These virus-specified components are often essential for virus replication and may be suitable targets for antiviral drug discovery strategies.

One such target that plays a central role in the life cycle of many RNA viruses is the virus-encoded RNA-dependent RNA polymerase (RdRp) protein. Regarding viruses of the Flaviviridae, this protein is termed NS5B in the case of the hepaciviruses and pestiviruses, and NS5 in the case of the flaviviruses (collectively referred to as NS5). RdRp proteins

are a key component of the virus replicase complex, enabling the virus to replicate its RNA genome and produce progeny viruses. The RdRp of RNA viruses is an attractive target for antiviral drug development.

Summary of the Invention

In accordance with one aspect, the present invention provides compounds for preventing or treating viral infections and for preventing or treating diseases associated with viral infections in living hosts. The compounds of the invention have the following general structure:



(I)

wherein X represents a divalent linking moiety selected from the group consisting of -CH=N- and -CH=CR$_a$-;

R represents a radical selected from the group consisting of an unsubstituted or substituted alkyl (C_1-C_6) radical, an unsubstituted or substituted aryl (C_6-C_{14}) radical, an unsubstituted or substituted aralkyl (C_7-C_{15}) radical, an

unsubstituted or substituted heterocyclic radical, or a radical of the formula $-NR_a-X'-R_b$, wherein X' represents a valence bond or a divalent linking moiety selected from the group of $-C(=O)-$, $-S(=O)_2-$ or $-(CH_2)_n-$, n being an integer from 1 to 6;

R_a represents hydrogen or an unsubstituted or substituted alkyl (C_1-C_6) radical; R_b represents hydrogen, an unsubstituted or substituted alkyl (C_1-C_6) radical, an unsubstituted or substituted aryl (C_6-C_{14}) radical, an unsubstituted or substituted aralkyl (C_7-C_{16}) radical, an unsubstituted or substituted heterocyclic radical, an unsubstituted or substituted alicyclic (C_5-C_7) radical or a carbalkoxy radical;

R_1 represents an unsubstituted or substituted alkyl (C_1-C_6) radical;

the heterocyclic radical represented by R or R_b being at least one selected from the group of furan, thiophene, pyrrole, tetrazole, pyridine, piperidine, morpholine, pyrazole, pyridazine, triazole, pyrimidine, oxadiazole, thiadiazole, oxazole, isoxazole, isothiazole or azepane; the alkyl radical substituent(s) being at least one selected from the group of carboxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thiol or alkylthio; the aryl radical substituent(s) and the aralkyl radical substituent(s) being at least one selected from the group of a straight or branched chain, saturated or unsaturated aliphatic group having 1-6 carbon atoms, halogen, nitro, carboxy, hydroxy, hydroxyalkyl, perhaloalkyl, monohaloalkyl, dihaloalkyl,

alkoxy, perhaloalkoxy, phenylalkoxy, acyl, acyloxy, acyloxyalkyl, cyano, carbalkoxy, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonamido, carboxamido or alkanoylamino; the heterocyclic radical substituent(s) and the alicyclic radical substituents(s) being at least one selected from the group of a straight or branched chain, saturated or unsaturated aliphatic group having 1-6 carbon atoms, halogen, perhaloalkyl, monohaloalkyl, dihaloalkyl, alkoxy, acyl, acyloxy, acyloxyalkyl, phenylalkoxy, hydroxy, hydroxyalkyl, alkylsulfonate, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, carboxy, carbalkoxy, or an unsubstituted or substituted aryl (C_6-C_{14}) radical; the isomeric forms and the pharmaceutically acceptable salts of the above compound.

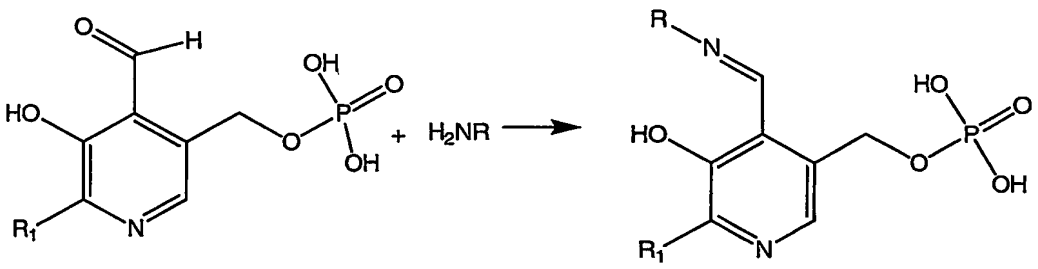
According to another aspect, the present invention provides pharmaceutical compositions comprising one or more of the above-described pyridine derivatives in combination with a pharmaceutically acceptable carrier medium.

In accordance with yet another aspect, the present invention provides methods for the treatment or prophylaxis of viral infections in living hosts by administering an effective amount of at least one compound of the invention to a host that is susceptible to, or suffering from such infection.

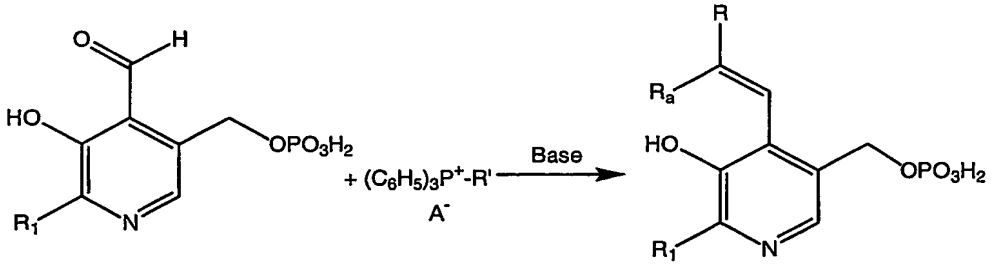
Detailed Description of the Invention

Pyridine derivatives according to the present invention can be conveniently prepared from known starting materials or from intermediates that may be prepared from known starting materials using conventional chemistry knowledge and skills, e.g. by following one of the general synthetic schemes shown below, wherein R, R_a and R^1 are as previously defined:

Scheme A



Scheme B



A = Anion, e.g., halogen
R' = -CHR_aR

E and/or Z isomers

In general synthetic scheme A, pyridoxal-5'-phosphate monohydrate is reacted with an amine reactant appropriate to yield the desired "R" substituent in the compound of formula (I), above. The reaction is conveniently conducted in a reaction medium, such as ethanol, heated to reflux for one to twelve hours.

General synthetic scheme B involves the reaction of pyridoxal phosphate with the appropriate triphenylphosphonium halide in the presence of *n*-butyl lithium or another appropriate base, such as a different carbanion, an alkoxide, or a metal hydride.

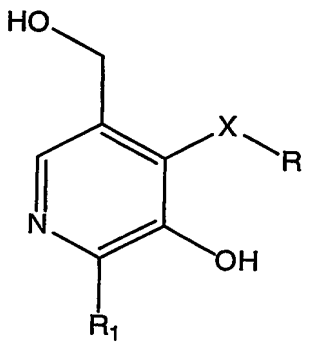
In the products obtained from the above-described reactions, the divalent linking moiety (X) is bound to the aromatic ring through a methine group.

Preparation of specific antiviral compounds which may be used in the practice of this invention are exemplified below. Starting materials for carrying out these reactions are available from commercial sources or are intermediates that may be prepared from known starting materials using conventional chemistry knowledge and skills.

In vitro studies have been performed which demonstrate the usefulness of compounds described herein as antiviral agents. Antiviral activity was measured by the inhibitory activity of the compounds against the viral RdRp in an enzymological assay for RNA synthesis.

Compounds having particular utility, including isomeric forms, are the pyridine derivatives shown in formula (I), above, in which X-R represents -C=N-aryl; -C=N-het; -C=N-NH-S(=O)$_2$-aryl; -C=N-NH-S(=O)$_2$-het; -C=N-NH-C(=O)-aryl; -C=N-NH-C(=O)-het; -C=N-NH-C(=O)-alkyl; -C=N-NH-C(=O)-H; -C=N-NH-aryl; -C=N-NH-aralkyl; -C=N-NH-het; -C=N-NH-cycloalkyl; and -C=N-NH-$(CH_2)_n$-C(=O)-O-alkyl (n=1-6), wherein "het" represents a heterocyclic radical, as previously defined with reference to formula I, above, and the heterocyclic radicals, the aryl radicals, the aralkyl radicals, the alkyl radicals, and the cycloalkyl radicals in this group of compounds may be unsubstituted or substituted, the heterocyclic radical substituent(s), the aryl radical substituent(s), the aralkyl radical substituent(s), and the alkyl radical substituents being as previously set forth with reference to formula I, above. The cycloalkyl radical substituents may be the same as the alicyclic radical substituents specified with reference to formula I, above.

Compounds of the invention also include those having the formula:

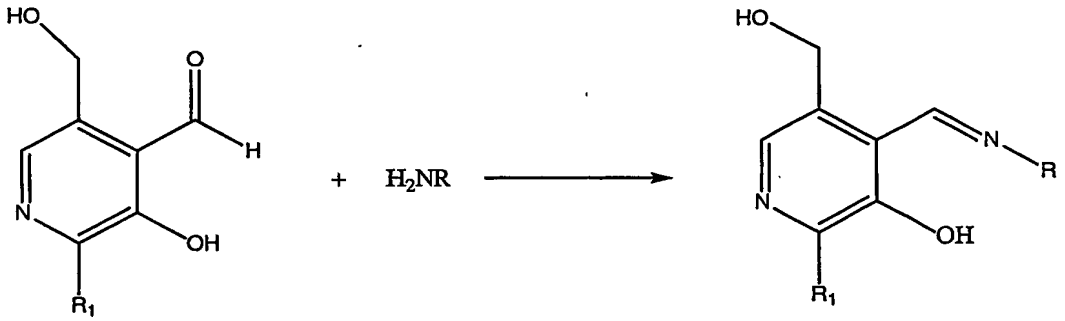


(II)

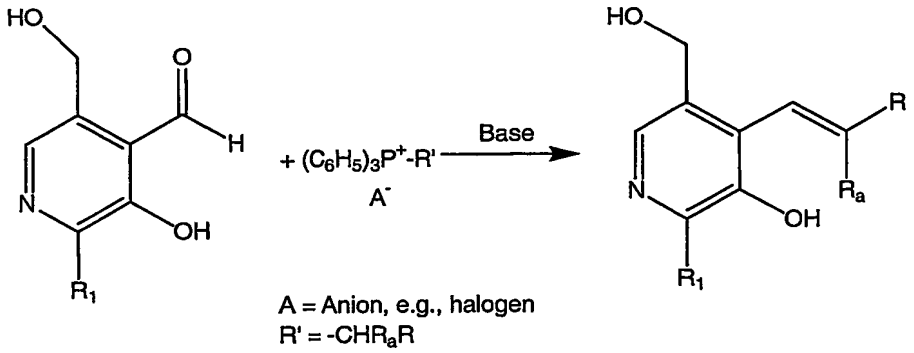
wherein, each of X, R_1, and R is as defined above, the isomeric forms of said compound and the pharmaceutically acceptable salts of said compound.

Compounds of formula II may be prepared by dephosphorylation of the corresponding compound of formula I, using methods and knowledge familiar to those of skill in the art. As previously noted, the compounds of formula I can be prepared from known starting materials, or from intermediates that can be prepared from known starting materials using conventional chemistry knowledge and skills. Alternatively, compounds of formula II may be synthesized according to Schemes C and D.

Scheme C



Scheme D

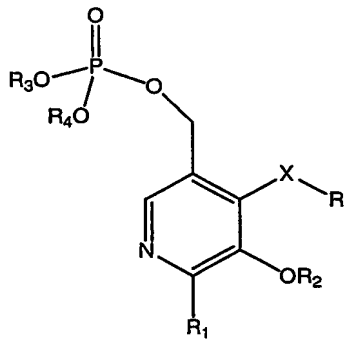


In schemes C and D, R, R_a and R_1 are as defined above. Scheme D illustrates a Wittig-type reaction analogous to that depicted in scheme B; therefore, the bases that are appropriate in the reaction of scheme B will also be appropriate in that of scheme D.

The compounds of the invention may be administered as such, or in a form from which the active agent can be derived, such as a prodrug. A prodrug is a derivative of a compound described herein, the pharmacologic action of which results from the conversion by chemical or metabolic processes *in vivo* to the active compound. Prodrugs include, without limitation, ester derivatives of the compounds of formula I, above. Carboxylate esters may be prepared, for example, by reacting simple or functionalized carboxylic acids with the hydroxyl group of the pyridine derivative. Other prodrugs may be prepared according to procedures well known in the field of medicinal chemistry and

pharmaceutical formulation science. *See, e.g.*, References 1 and 2, *below*.

Prodrugs, in accordance with the present invention, include, without limitation, compounds having the formula:



(III)

wherein X, R, and R_1 are as previously defined, and R_2, R_3 and R_4 may be the same or different, and represent hydrogen or a radical selected from the group consisting of substituted or unsubstituted, straight or branched chain alkyl (C_1-C_6), substituted or unsubstituted alicyclic (C_5-C_7), substituted or unsubstituted aryl (C_6-C_{14}) radicals, an acyl radical, an acyloxyalkyl radical or an amino acid residue (-C(=O)-CHR_c-NH_2, wherein R_c is the side chain of a naturally occurring amino acid), the isomeric forms of said compound and the pharmaceutically acceptable salts of said compound.

The substituted alkyl, alicyclic and aryl radicals represented by R_2, R_3, and R_4 are the same as previously described, with reference to the compounds of Formula I.

Prodrugs of formula III may be synthesized from known starting materials or from intermediates that can be prepared

from known starting materials using conventional chemistry knowledge and skills. *See also* the References listed below.

Although compounds of formula III may serve as prodrugs in accordance with this invention, their utility is not so limited. For example, compounds of formula III, *per se*, exhibit pharmaceutical activity. Furthermore, compounds of formula III may also serve as intermediates in the synthesis of compounds of formula I by reactions that are familiar to those of skill in the art.

The term "aryl" as used herein refers to a carbocyclic, aromatic radical of six to fourteen carbon atoms and includes, without limitation, phenyl, naphthyl, fluorenyl, anthracenyl, indanyl or the like.

The term "alkyl" as used herein refers to aliphatic hydrocarbon radicals of one to six carbon atoms in length. Similarly, the term "alkyl", or any variation thereof, used in combination form to name substituents, such as aralkyl, phenylalkyl, alkoxy, alkylthio, alkylamino, alkylsulfinyl or alkylsulfonyl also refers to aliphatic hydrocarbon radicals of one to six carbon atoms in length.

The term "acyl", or any variation thereof, used in combination form to name substituents, e.g. acyloxyalkyl, refers to a radical which is derived from a carboxylic acid by the removal of the hydroxyl groups, and which may be either aliphatic (straight or branched chain C_1-C_6) or aromatic (C_6-C_{14}).

The term "carboxamido", as used herein, refers to a radical or substituent of the formula -C(=O)-NR"R"', wherein R" and R"' represent hydrogen or alkyl (C_1-C_6).

The term "sulfonamido", as used herein, refers to a radical or substituent of the formula -SO_2-NR"R"' or -NR"-SO_2R"', wherein R" and R"' are as previously defined.

The term "alkanoylamino", as used herein, refers to a radical or substituent of the formula -NH-C(=O)-R", wherein R" is as previously defined.

The term "carbalkoxy", as used herein, refers to a radical or substituent -C(=O)-OR", wherein R" is as previously defined.

The compounds of formula I, II, and III, above, their isomers and their pharmaceutically acceptable salts exhibit antiviral activity. The compounds of the invention are particularly effective against viruses of the Flaviviridae family and are useful in the treatment and prophylaxis of infections and diseases associated with these viruses in living hosts.

The compounds of the present invention or precursors thereof and their isomeric forms and pharmaceutically acceptable salts thereof are also useful in treating and preventing viral infections, in particular hepatitis C infection, and diseases in living hosts when used in combination with each other (i.e. pharmaceutical compositions comprising the compounds are administered concurrently with each other or sequentially, in either order). The combination of compounds provided herein may

further be provided to a subject in respective pharmaceutical compositions, concurrently with or sequentially to other biologically active agents, including but not limited to the group consisting of interferon, a pegylated interferon, ribavirin, protease inhibitors, polymerase inhibitors, small interfering RNA compounds, anti-sense compounds, nucleotide analogs, nucleoside analogs, immunoglobulins, immunomodulators, hepatoprotectants, anti-inflammatory agents, antibiotics, antivirals, and anti-infective compounds. The present invention further provides combination therapy in which two or more pyridine derivatives, i.e., at least two pharmaceutical compositions, each comprising a different compound of the present invention, are provided to a subject in need thereof either concurrently with each other or sequentially, and such therapy may further comprise providing concurrently or sequentially other therapeutic agents or potentiators, such as acyclovir, famicyclovir, valgancyclovir and related compounds, ribavirin and related compounds, amantadine and related compounds, various interferons such as, for example, interferon-alpha, interferon-beta, interferon-gamma and the like, as well as alternative forms of interferons such as pegylated interferons. Additionally, combinations of, for example ribavirin and interferon, may be administered as an additional combination for a multiple combination therapy with at least one of the compounds of the present invention.

The combination therapy with any of the above-described

biologically active agents may also be sequential, that is the treatment with a first pharmaceutical composition comprising a compound of the invention followed by treatment with a second pharmaceutical composition comprising a second compound of the invention, wherein the second compound is different than the first compound. Alternatively, treatment may be with both two or more pharmaceutical compositions, wherein each pharmaceutical composition comprises a different compound of the invention, at the same time. The sequential therapy can be within a reasonable time after the completion of the first therapy with the pharmaceutical composition. Treatment with the respective pharmaceutical compositions, each comprising a different compound of the present invention, at the same time may be provided in the same daily dose or in separate doses. Combination therapy may also be provided wherein a pharmaceutical composition comprising at least one compound of the present invention is administered in a composition further comprising at least one biologically active agent, i.e. in a single dose. The dosages for both concurrent and sequential combination therapy (for combined pharmaceutical compositions comprising at least two compounds of the invention or compositions comprising at least one compound of the invention and at least one biologically active agent), will depend on absorption, distribution, metabolism and excretion rates of the components of the pharmaceutical composition as well as other factors known to one of skill in the art. Dosage values of the pharmaceutical composition will also vary with the

severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules may be adjusted over time according to the individual's need and the professional judgment of the person administering or supervising the administration of the pharmaceutical compositions.

In a further embodiment, the compounds of the invention may be used for the treatment of HCV in humans in combination therapy mode with other inhibitors of the HCV polymerase.

In yet a further embodiment, the compounds of the present invention may be used for the treatment of HCV in humans in combination therapy mode with other inhibitors of the HCV life cycle such as, for example, inhibitors of HCV cell attachment or virus entry, HCV translation, HCV RNA transcription or replication, HCV maturation, assembly or virus release, or inhibitors of HCV enzyme activities such as the HCV nucleotidyl transferase, helicase, protease or polymerase.

It is intended that combination therapies of the pharmaceutical compositions include any chemically compatible combination of a compound of this inventive group with other compounds of the inventive group or other compounds outside of the inventive group, as long as the combination does not inhibit or eliminate the anti-viral activity of the compound of this inventive group or the anti-viral activity of the pharmaceutical composition itself.

The term "interferon-alpha" as used herein means the

family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alphas include, but are not limited to, recombinant interferon alpha-2b, such as INTRON-A INTERFERON available from Schering Corporation, Kenilworth, NJ; recombinant interferon alpha-2a, such as Roferon interferon available from Hofman-La Roche, Nutley, NJ; a recombinant interferon alpha-2C, such as BEROFOR ALPHA 2 INTERFERON available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, Conn., interferon alpha-n1, a purified blend of natural alpha interferons, such as SUMIFERON available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon, such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (the contents of which are hereby incorporated by reference in their entireties herein specifically examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, Calif., or interferon alpha-n3 a mixture of natural interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, Conn., under the ALFERON trademark. The use of interferon alpha-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Pat. No. 4,503,901 (the content of which is hereby incorporated by

reference in its entirety herein).

The term "pegylated interferon" as used herein means polyethylene glycol modified conjugates of interferon, preferably interferon alpha-2a and alpha-2b. The preferred polyethylene-glycol-interferon alpha-2b conjugate is PEG.sub.12000-interferon alpha 2b. The phrase "PEG.sub.12000-IFN alpha" as used herein means conjugates such as are prepared according to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alpha-2a or alpha-2b amino groups and polyethylene glycol having an average molecular weight of 12000 (the content of WO 95/13090 is hereby incorporated by reference in its entirety herein).

Compounds described herein are also useful in preventing or resolving viral infections in cell, tissue or organ cultures and other *in vitro* applications. For example, inclusion of compounds of the invention as a supplement in cell or tissue culture growth media and cell or tissue culture components will prevent viral infections or contaminations of cultures not previously infected with viruses. Compounds described above may also be used to eliminate viruses from cultures or other biological materials infected or contaminated with viruses (e.g., blood), after a suitable treatment period, under any number of treatment conditions as determined by the skilled artisan.

Compounds of the invention can form useful salts with inorganic and organic acids such as hydrochloric, sulfuric, acetic, lactic, or the like, and with inorganic or organic bases

such as sodium or potassium hydroxide, piperidine, ammonium hydroxide, or the like. The pharmaceutically acceptable salts of the compounds of formula I, II, and III, above, are prepared following procedures that are familiar to those skilled in the art.

All isomeric forms of the above-described compounds are within the scope of the invention, including, without limitation, the various isomers of the heterocyclic substituents that may be present therein, as well as tautomeric forms thereof, and *cis* and *trans* isomers. One or both of the *cis* and *trans* isomers may be synthesized about any given non-cyclic double bond and such isomers constitute preferred embodiments of the present invention.

The antiviral pharmaceutical compositions of the present invention comprise one or more of the compounds of formula I, II, and III, above, as the active ingredient, and, optionally, at least one supplemental active agent, in combination with a pharmaceutically acceptable carrier medium or auxiliary agent.

The composition may be prepared in various forms for administration, including tablets, caplets, pills or dragees, or can be filled in suitable containers, such as capsules, or, in the case of suspensions, filled into bottles. As used herein, "pharmaceutically acceptable carrier medium" includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents,

thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Eighteenth Edition, E.W. Martin (Mack Publishing Co., Easton, PA, 1990) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the antiviral compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

In the pharmaceutical compositions of the invention, the active ingredient may be present in an amount of at least 0.5% and generally not more than 90% by weight, based on the total weight of the composition, including carrier medium and/or supplemental active agent(s), if any. Preferably, the proportion of active agent varies between 2-50% by weight of the composition.

Pharmaceutical organic or inorganic solid or liquid carrier media suitable for enteral or parenteral administration can be used to make up the composition. Gelatine, lactose, starch, magnesium, stearate, talc, vegetable and animal fats and oils, gum, polyalkylene glycol, or other known medicament components may all be suitable as carrier media or excipients.

The compounds of the invention may be administered

using any amount and any route of administration effective for attenuating infectivity of the virus. Thus, the expression "amount effective to attenuate infectivity of virus", as used herein, refers to a nontoxic but sufficient amount of the antiviral agent to provide the desired treatment of viral infection. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of infection, the particular antiviral agent, its mode of administration, and the like.

The antiviral compounds are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form" as used herein refers to a physically discrete unit of antiviral agent appropriate for the subject to be treated. Each dosage should contain the quantity of active material calculated to produce the desired therapeutic or prophylactic effect either as such, or in association with the selected pharmaceutical carrier medium and/or the supplemental active agent(s), if any. Typically, the antiviral compounds of the invention will be administered in dosage units containing from about 0.1 mg to about 500 mg of the antiviral agent by weight of the composition, with a range of about 1 mg to about 100 mg being preferred.

The compounds may be administered orally, rectally, parenterally, such as by intramuscular injection, subcutaneous injection, intravenous infusion or the like, intracisternally, intravaginally, intraperitoneally, locally, such as by powders,

ointments, drops or the like, or by inhalation, such as by aerosol or the like, depending on the nature and severity of the infection being treated. Depending on the route of administration, the compounds of the invention may be administered at dosage levels of about 0.001 to about 120 mg/kg of subject body weight per day and preferably from about 0.01 to about 30 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. By way of example, a suitable dose for oral administration would be on the order of 20 mg/kg of body weight per day, whereas a typical dose for intravenous administration would be on the order of 10 mg/kg of body weight per day.

The compounds of the invention will typically be administered from 1 to 4 times a day so as to deliver the above-mentioned daily dosage. However, the exact regimen for administration of the compounds and compositions described herein will necessarily be dependent on the needs of the individual host being treated, the type of treatment administered and the judgment of the attending medical specialist. As used herein, the terms "host" and "subject" include both humans and animals.

In view of the inhibitory effect on viral RNA synthesis produced by the compounds of the invention, it is anticipated that these compounds will be useful not only for therapeutic treatment of virus infection, but for virus infection prophylaxis, as well. The dosages may be essentially the same, whether for treatment or prophylaxis of virus infection.

The following examples are provided to describe the invention in further detail. These examples, which set forth a preferred mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Examples 1-3 illustrate suitable methods of synthesis of representative compounds of this invention. However, the method of synthesis is not limited to those exemplified below.

Example 1

Phosphoric acid mono-(5-hydroxy-6-methyl-4-[2-methyl-1-tetrazolylimino]methyl-pyridin-3-ylmethyl)ester

A mixture of 99.0 mg (1 mmole) of 1-amino-2-methyltetrazole and 265 mg (1 mmole) of pyridoxal-5'-phosphate monohydrate in 5 ml of ethanol was heated to reflux for 30 min. A yellow solid formed. To the mixture was added 4 ml of water and the mixture cooled to room temperature and the solid collected by filtration, washed with ethanol and dried to yield 246 mg of product.

Example 2

Phosphoric acid mono-(5-hydroxy-6-methyl-4-[2-napthylimino] methyl-pyridin-3-ylmethyl)ester

A mixture of 143 mg (1 mmole) of 2-aminonapthalene and 265 mg (1 mmole) of pyridoxal-5'-phosphate in 12 ml of ethanol was heated to reflux for 6 hours. The mixture was diluted with 10 ml of water and the resulting solid collected by filtration, washed with ethanol and dried.

Example 3

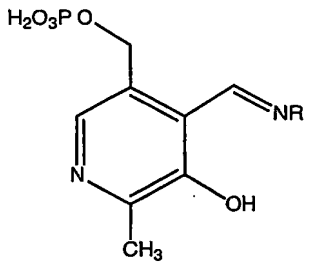
3-hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde phenylsulfonylhydrazone

A mixture of 172 mg (1 mmoles) of benzenesulfonylhydrazine, 124 mg (.5 mmoles) of pyridoxal phosphate monohydrate and 19 mg (.1 mmoles) of p-toluenesulfonic acid in 17 ml of water were heated to 70°C for 5 hours. After

cooling, water was added and the solid was collected by filtration, washed with water and dried to give 85 mg of product as a light yellow solid.

By appropriate selection of suitable reactants, other compounds of the invention may be prepared according to the above-described reaction schemes and the procedures set forth in the foregoing examples. Representative examples of further pyridine derivatives thus prepared are set forth in Table 1A, below. The compounds listed in Table 1A have the structure of formula I, in which the X moiety is -CH=N-.

Table 1A



Example No.	R	Compound Name
4	Ph*	Phosphoric acid mono-(5-hydroxy-6-methyl-4-[phenylimino]methyl-pyridin-3-ylmethyl)ester

5	NH-S(=O)$_2$-2,4,6-tri CH_3-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2,4,6-trimethyl phenyl sulfonyl hydrazone
6	NH-C(=O)-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-benzoyl hydrazone
7	NH-3-F-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-3-fluorophenyl hydrazone
8	NH-C(=O)-C_4H_3O	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2-furoyl hydrazone
9	NH-C(=O)-4-Cl-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-4-chlorobenzoyl hydrazone
10	NH-C(=O)-CH_3	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-acetyl hydrazone
11	NH-C(=O)-H	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-formyl hydrazone
12	NH-3-NO_2-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-3-nitrophenyl hydrazone
13	NH-C(=O)-3-Cl-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-3-chlorophenyl hydrazone
14	NH-C(=O)-C_4H_3S	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2-thenoyl hydrazone
15	NH-C(=O)-4-NO_2-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-3-nitrobenzoyl hydrazone

16	NH-C_6H_{11}	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-cyclohexane hydrazone
17	NH-CH_2-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-benzyl hydrazone
18	NH-C(=O)-2-OCH_3-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2-methoxybenzoyl hydrazone
19	NH-C(=O)-3-OC_2H_5-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-3-ethoxybenzoyl hydrazone
20	NH-C(=O)-2-NO_2-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2-nitrobenzoyl hydrazone
21	NH-C(=O)-1-CH_3-2-pyrrole	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-1-methyl-2-pyrrolecarbonyl hydrazone
22	NH-C(=O)-4-pyridine	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-isonicotinoyl hydrazone
23	NH-2-F-Ph	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-2-fluorophenyl hydrazone
24	NH-CH_2-C(=O)-OC_2H_5	3-Hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridine carboxaldehyde-carbethoxmethyl hydrazone
25	NH-S(=O)$_2$-CH_3	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde methylsulfonylhydrazone

26	NH-S(=O)$_2$-4-OCH$_3$-Ph	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl-4-pyridine carboxaldehyde-4-methoxyphenyl sulfonyl hydrazone
27	NH-S(=O)$_2$-4-F-Ph	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde-4-fluorophenylhydrazone
28	NH-S(=O)$_2$-4-CH$_3$-Ph	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde-4-methylphenylhydrazone
29	NH-S(=O)$_2$-4-CH$_3$-C(=O)-NH-Ph	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde-4-acetylaminephenyl hydrazone
30	NH-S(=O)$_2$-4-t-butyl-Ph	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde-4-t-butylphenylhydrazone
31	NH-S(=O)$_2$-2-N(CH$_3$)$_2$-6-Nap**	3-Hydroxy-2-methyl-5-[(phosphonoxy)methyl]-4-pyridine carboxaldehyde-2-dimethylamino napthyl hydrazone

* Ph = phenyl (C_6H_5-)

** Nap = napthyl ($C_{10}H_7$-)

Example 32

Phosphoric acid mono-(5-hydroxy-6-methyl-4-styryl-pyridin-3-ylmethyl)ester

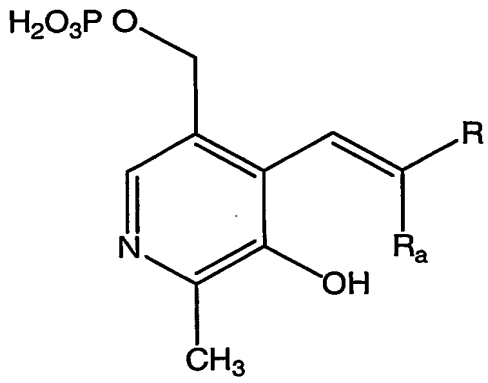
106 mg (2.6 mmol) of sodium hydride (as a 60% dispersion in mineral oil) was added to 10 ml anhydrous DMSO and allowed to stir at room temperature, under argon, for one hour. To the mixture was added 807 mg (2.1 mmol) of benzyltriphenylphosphonium chloride in three portions over 15

minutes. A second solution was prepared by dissolving 500 mg (1.9 mmol) of pyridoxal-5-phosphate monohydrate in 5ml DMSO with heating. 3 Å molecular sieves were added to this solution to exclude water. This second solution was added to the reaction mixture over 10 minutes, and the resulting mixture was stirred at room temperature overnight.

The mixture was poured over 100 ml of water, and 1 M NaOH was added until a pH of 9-10 was reached. The mixture was extracted first with t-butyl methyl ether and then with methylene chloride. The aqueous layer was acidified with acetic acid and extracted with ethyl acetate. This aqueous layer was saturated with sodium chloride. The resulting precipitate was collected by filtration, washed with a small amount of water and t-butyl methyl ether, and dried to yield 140 mg of product.

Additional representative examples of pyridine derivatives of the invention are set forth in Table 1B, below. The compounds listed in Table 1B have the structure of formula I, in which the X moiety is $-CH=CR_a-$.

Table 1B



Example No.	R_a	R	Compound Name
33	H	H	Phosphoric acid mono-(5-hydroxy-6-methyl-4-vinyl-pyridin-3-ylmethyl)ester
34	H	CH_3	Phosphoric acid mono-(5-hydroxy-6-methyl-4-propenyl-pyridin-3-ylmethyl) ester
35	CH_3	CH_3	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(2-methyl-propenyl)-pyridin-3-ylmethyl)ester
36	CH_3	Ph	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(2-phenyl-propenyl)-pyridin-3-ylmethyl)ester
37	H	PhMe	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(4-methylstryl)-pyridin-3-ylmethyl)ester
38	H	Ph CF_3	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(4-trifluoromethylstryl)-pyridin-3-ylmethyl)ester
39	H	Ph-OCF_3	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(4-trifluoromethoxystryl)-pyridin-3-ylmethyl)ester
40	H	PhF	Phosphoric acid mono-(5-hydroxy-6-methyl-4-(4-fluorostryl)-pyridin-3-ylmethyl)ester

Example 41

Inhibition of Viral RNA Replication

The discovery of inhibitors of viral polymerases and related proteins generally requires the evaluation of large numbers of chemical compounds or mixtures of chemical compounds. Thus, an assay for the polymerase activity that is capable of high volume screening, in other words, a high-throughput assay, is desirable. There are a variety of assay methodologies well known to the trained artisan that allow the efficient screening of large numbers of samples. See, for example, Cole, JL, Meth Enzymology, 275: 310-328 (1996). Any one of these assays may be suitable in the case of a viral RdRp activity.

One approach for measuring viral RdRp activity in the case of viruses of the Flaviviridae utilizes a purified recombinant NS5 protein in an *in vitro* RdRp assay. For example, Behrens et al. [EMBO J., 15: 12-22 (1996)] and Lohmann et al. [J Virol, 71:8416-8428 (1997)] describe the baculovirus expression, purification and enzymatic activity of the HCV NS5B RdRp. The bacterial expression, purification and enzymatic activity of the HCV NS5B RdRp protein has been disclosed in PCT/US96/15571 [WO 97/12033] and by Yuan et al. [Bioochem Biophys Res Comm, 232:231-235 (1997)]. In a further example, Collett, PCT/US99/07404, [WO 99/51781], which is commonly owned with the present application, discloses compositions comprising functional HCV NS5B sequences and their use in identifying compounds useful in the treatment of hepacivirus infections. As with the above examples for the

HCV RdRp, bacterially-expressed dengue flavivirus NS5 protein has been purified and shown to exhibit RdRp activity [Tan et al., Virology, 216: 317-325 (1996)], as has the NS5B protein of the pestivirus BVDV purified from recombinant baculovirus-infected cells [Zhong et al., J. Virol., 72: 9365-9369 (1998)].

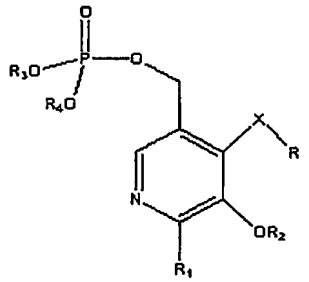
By way of example, the inhibitory activity of candidate compounds within the scope of this invention was demonstrated in *in vitro* RdRp assays using NS5 proteins prepared essentially according to Collett, PCT/US99/07404, the entire disclosure of which is incorporated by reference herein. Purified NS5 proteins are incubated in standard RdRp reaction mixtures. Such reaction mixtures generally consist of buffers, salts, cations, reducing agents and the like, as well as nucleoside triphosphates and an RNA template-primer. Variations in the individual components of such reaction mixtures may be required to accommodate the particular reaction preferences of individual NS5 proteins. Such variations are well known to the trained artisan.

Representative compounds within the scope of the present invention, as shown in Examples 1-3 and the foregoing table, were evaluated for antiviral activity in this assay. Inhibitory activity of the compounds tested was expressed in IC_{50} values. IC_{50} values represent the concentration of the compound at which 50% of the RdRp activity is inhibited. The results of the assay for inhibition of RdRp activity in at least one virus of the Flaviviridae family for the compounds tested revealed IC_{50} values ranging from 0.08 to about 30 μM. The low concentrations

of test compounds capable of achieving 50% inhibition of the RdRp activity indicate that the compounds of the invention are effective at inhibiting RNA synthesis by viral RdRp enzymes involved in Flaviviridae replication.

The following table contains examples of prodrugs of Formula III which may be synthesized using conventional chemistry knowledge. *See, e.g.*, the References section, below. In the following examples, X, R, and R_1 are as previously defined.

Table 2



(II)

Example No.	R_2	R_3	R_4
42	$-C(=O)CH_3$	H	H
43	$-C(=O)Ph$	H	H
44	$-C(=O)CH_3$	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H

45	-C(=O)Ph	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H
46	-C(=O)CH_3	phenyl	H
47	-C(=O)Ph	phenyl	H
48	-C(=O)CH_3	ethyl	H
49	-C(=O)Ph	ethyl	H
50	-C(=O)CH_3	cyclohexyl	H
51	-C(=O)Ph	cyclohexyl	H
52	-C(=O)CH_3	phenyl	phenyl
53	-C(=O)Ph	phenyl	phenyl
54	-C(=O)CH_3	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.

55	-C(=O)Ph	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.
56	Residue of an amino acid selected from the group consisting of alanine, valine leucine, isoleucine, proline, phenylalanine, tryptophan and methionine.	H	H
57	Alanine	H	H
58	Valine	H	H
59	Leucine	H	H

60	Residue of an amino acid selected from the group consisting of glycine, serine, threonine, cysteine, tyrosine, asparagines and glutamine.	H	H
61	Glycine	H	H
62	Serine	H	H
63	Threonine	H	H
64	Residue of an amino acid selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine and histidine.	H	H
65	Aspartic acid	H	H
66	Glutamic acid	H	H
67	Lysine	H	H

68	Residue of an amino acid selected from the group consisting of alanine, valine leucine, isoleucine, proline, phenylalanine, tryptophan and methionine.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H
69	Alanine	phenyl	H
70	Valine	phenyl	H
71	Leucine	phenyl	H
72	Residue of an amino acid selected from the group consisting of glycine, serine, threonine, cysteine, tyrosine, asparagines and glutamine.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H
73	Glycine	phenyl	H
74	Serine	phenyl	H
75	Threonine	phenyl	H

76	Residue of an amino acid selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine and histidine.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H
77	Aspartic acid	phenyl	H
78	Glutamic acid	phenyl	H
79	Lysine	phenyl	H
80	Residue of an amino acid selected from the group consisting of alanine, valine leucine, isoleucine, proline, phenylalanine, tryptophan and methionine.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.
81	Alanine	phenyl	phenyl
82	Valine	phenyl	phenyl
83	Leucine	phenyl	phenyl

84	Residue of an amino acid selected from the group consisting of glycine, serine, threonine, cysteine, tyrosine, asparagines and glutamine.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.
85	Glycine	phenyl	phenyl
86	Serine	phenyl	phenyl
87	Threonine	phenyl	phenyl
88	Residue of an amino acid selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine and histidine.	A substitutent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.
89	Aspartic acid	phenyl	phenyl
90	Glutamic acid	phenyl	phenyl
91	Lysine	phenyl	phenyl

92	Residue of an amino acid selected from the group consisting of alanine, valine leucine, isoleucine, proline, phenylalanine, tryptophan and methionine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	H
93	Alanine	CH(iPr)O(CO)n-heptyl	H
94	Valine	CH(iPr)O(CO)n-heptyl	H
95	Leucine	CH(iPr)O(CO)n-heptyl	H
96	Residue of an amino acid selected from the group consisting of glycine, serine, threonine, cysteine, tyrosine, asparagines and glutamine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	H
97	Glycine	CH(iPr)O(CO)n-heptyl	H
98	Serine	CH(iPr)O(CO)n-heptyl	H
99	Threonine	CH(iPr)O(CO)n-heptyl	H

100	Residue of an amino acid selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine and histidine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	H
101	Aspartic acid	CH(iPr)O(CO)n-heptyl	H
102	Glutamic acid	CH(iPr)O(CO)n-heptyl	H
103	Lysine	CH(iPr)O(CO)n-heptyl	H
104	Residue of an amino acid selected from the group consisting of alanine, valine leucine, isoleucine, proline, phenylalanine, tryptophan and methionine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl
105	Alanine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
106	Valine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
107	Leucine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl

108	Residue of an amino acid selected from the group consisting of glycine, serine, threonine, cysteine, tyrosine, asparagines and glutamine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl
109	Glycine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
110	Serine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
111	Threonine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
112	Residue of an amino acid selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine and histidine.	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl
113	Aspartic acid	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
114	Glutamic acid	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl
115	Lysine	CH(iPr)O(CO)n-heptyl	CH(iPr)O(CO)n-heptyl

116	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	H
117	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.
118	H	phenyl	H
119	H	phenyl	ethyl
120	H	ethyl	H
121	H	ethyl	phenyl
122	H	cyclohexyl	H
123	H	cyclohexyl	ethyl
124	H	phenyl	phenyl
125	H	phenyl	cyclohexyl

126	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	cyclohexyl
127	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	(4-methyl)phenyl
128	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	ethyl
129	H	ethyl	ethyl
130	H	cyclohexyl	cyclohexyl
131	H	(4-methyl)phenyl	(4-methyl)phenyl

132	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	phenyl
133	H	(4-n-propyl)phenyl	(4-n-propyl)phenyl
134	H	(4-isopropyl)phenyl	(4-isopropyl)phenyl
135	H	(3,4-dimethyl)phenyl	(3,4-dimethyl)phenyl
136	H	A substituent selected from the group consisting of C_1-C_6-alkyl, cyclohexyl, phenyl, (4-methyl)phenyl, (4-n-propyl)phenyl, (4-isopropyl)phenyl, (3,4-dimethyl)phenyl, (3,5,-dimethyl)phenyl, indanyl, (3-methoxyphenyl) and (4-methoxy)phenyl.	C_1-C_6-alkyl
137	H	(3,5-dimethyl) phenyl indanyl	(3,5-dimethyl) phenyl indanyl
138	H	C_1-C_6-alkyl	C_1-C_6-alkyl
139	H	(4-methoxy)phenyl	(4-methoxy)phenyl

140	H	A substituent selected from the group consisting of $CH_2O(CO)$t-butyl, $CH_2O(CO)$isopropyl, CH(Me)O(CO)ethyl, CH(iPr)O(CO)ethyl, CH(cHex)O(CO)ethyl, CH(iPr)O(CO)isopropyl, and CH(iPr)O(CO)n-heptyl	H
141	H	CH(iPr)O(CO)n-heptyl	H
142	H	CH(iPr)O(CO)n-heptyl	H
143	H	CH(iPr)O(CO)n-heptyl	H

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

References

The following publications are incorporated by reference herein in their entirety.

1. Lombaert et al., J. Med. Chem., Vol. 37, p.498-511 (1994).

2. Vepsalainen, Tet. Letters, Vol. 40, p. 8491-8493 (1999).

3. Sawaki et al.,*The Effect of Pyridoxal Phosphate on Type C Hepatitis*, Medicine and Biology, Vol. 135, No. 1, p. 13-15 (1997).

4. Sawaki et al., Effect of Pyridoxal Phosphate Administration on Hepatitis C Virus RNA in Patients with Hepatitis Type C, Vol. 135, No. 4, p. 149-151 (1997).